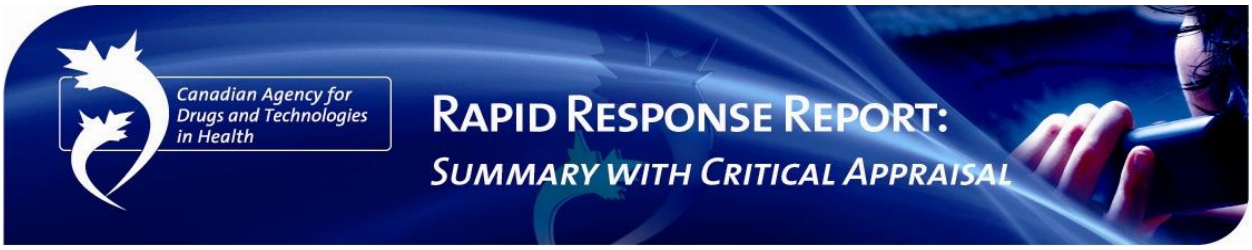

TITLE: Folate Testing: A Review of the Diagnostic Accuracy, Clinical Utility, Cost-Effectiveness and Guidelines

DATE: 23 July 2015

CONTEXT AND POLICY ISSUES

Folate is an essential micronutrient abundant in foods such as dark green vegetables and legumes. It is also consumed as synthetic folic acid in supplements and fortified foods. Folate is water-soluble so a constant dietary supply is required to support its metabolic role as a 1-carbon donor. This function is essential for DNA and amino acid synthesis, thus deficiency manifests in rapidly overturning red blood cells (RBC) as megaloblastic anemia. Adequate folate status is of particular importance during pregnancy as deficiency is associated with an increased risk of congenital malformations.[1] Risk factors for folate deficiency are plentiful and relate to inadequate intake, impaired absorption (e.g., gastrointestinal conditions), increased requirements (e.g., during pregnancy), and lifestyle (e.g., alcohol abuse) and genetic factors.[2,3]

In clinical practice, serum and RBC folate assays are utilized in folate assessment. Complete blood counts are often conducted alongside these tests to assess deficiency symptoms, and homocysteine concentrations can be assessed as a non-specific indicator of functional folate status. Measurement of serum folate requires fewer analytical hurdles than RBC folate and is sensitive to dietary intake.[4] However, RBC folate provides a more accurate representation of long-term status.[5] It has been proposed that serum folate provides equivalent clinical value to RBC folate in the majority of cases.[6] Yet, there is discordance among pathology authorities regarding the optimal assay to use.[7] Further, inter-assay and inter-laboratory variability of folate status measurement is high and lack of standardization has caused confusion when comparing studies.[8,9] Current guidelines that address folate testing are primarily targeted towards specific clinical populations with known risk of deficiency. In 2013, the Ontario Health Technology Advisory Committee made recommendations based on expert opinion that folate testing be restricted to individuals with abnormal hematological profiles and suspected gastrointestinal disorders associated with malabsorption.[10] Widely applied clinical practice guidelines produced by the Joint Society of Obstetricians and Gynecologists of Canada state that folate testing is not required for pregnant women prior to initiating supplementation.[1]

Since the advent of universal fortification of wheat flour with folic acid in Canada in 1998, the rate of folate deficiency has decreased substantially, as have the rates of adverse health outcomes associated with poor folate status.[11] The latest Canadian Health Measures Survey reported folate deficiency in less than 1% of the Canadian population.[12] Concerns have been raised about the volume of folate testing in developed countries with fortification.[13] Pre-fortification data from the Institute for Clinical and Evaluative Sciences (ICES) in Canada showed 7.92 million dollars in spending on folate testing between 1994 and 1995 and a temporal increase in the rate of testing.[14] Post-fortification, some jurisdictions have attempted to scale back. For instance, Manitoba restricted testing to a single clinical center and advised against testing to investigate anemia.[15] Prince Edward Island has phased out all testing due to the low rates of deficiency and the option to supplement based on clinical opinion.[16] Recent data from Australia shows a persistence in use with an increase (+119%) over the period from 2004 to 2014.[13] Since 2007, the rate of folate testing in the community has decreased in Ontario, but spending is still high.[10] Over the 2011/2012 period, just under 5 million dollars were spent on folate testing.[10] A review of red blood cell folate tests performed on all inpatients at the University Health Network sites in Toronto showed that less than 1% of RBC folate tests were deficient and that $32,000 dollars could be saved within this hospital network alone by limiting testing of inpatients.[17]

Reductions in folate testing have been proposed on the basis of low levels of deficiency in fortified populations.[17,18] The very low deficiency rate in Canada signals that reconsideration of the necessity of folate testing nationwide may be required, particularly in populations that could potentially benefit from targeted supplementation. Supplementation has not been linked to any adverse side-effects apart from potentially masking underlying vitamin B12 deficiency, and possible central nervous system and gastrointestinal side effects at 15 times the current tolerable upper limit of 1000 micrograms; however, the potential harms of foregoing testing for supplementation are unknown. The direct cost of folate testing is substantially higher than supplementation, although no formal cost-effectiveness analyses have been conducted.[19] As well, the clinical utility of folate testing is unclear.

This review will address lack of clarity surrounding the clinical utility and resource implications of folate testing, as well as the uncertainty regarding the appropriate analytical methods and clinical indications for routine folate testing.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of red blood cell folate versus serum folate testing for identifying folate deficiency?

2. What is the comparative clinical utility of red blood cell folate versus serum folate testing?

3. What is the clinical utility of folate testing?

4. What is the cost-effectiveness of folate testing?

5. What are the evidence-based guidelines regarding appropriate indications for folate testing?

6. What are the evidence-based guidelines regarding which assay to use for folate testing?

KEY FINDINGS

There is insufficient evidence to support the clinical utility of folate testing in patients at risk of folate deficiency, particularly in folic acid fortified regions. Evidence-based guidelines provide recommendations based primarily on low quality evidence and expert consensus to support the use of folate testing in specific clinical populations. There was general agreement among several guidelines that serum folate is preferable to RBC folate; however, no evidence was identified the diagnostic accuracy or comparative clinical utility of the respective assays. The resource implications of folate testing are unclear.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and June 19, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Any adult or pediatric population
Intervention	Q1 and 2: Red blood cell folate testing Q3 to 6: Any folate assay (e.g., serum folate, red blood cell folate)
Comparator	Q1 and 2: Serum folate testing Q3 and 4: Any alternate folate assay; Homocysteine testing; No testing; No comparator Q5 and 6: No comparator
Outcomes	Q1: Diagnostic accuracy outcomes Q2 and 3: Clinical utility outcomes (e.g., improved folate status or clinical condition [e.g., anemia symptoms, rate of congenital

	malformations] subsequent to identified need for supplementation) Q4: Cost-effectiveness outcomes Q5: Guidelines and recommendations regarding which populations should be tested for folate deficiency Q6: Guidelines and recommendations regarding which folate assay to use when testing for folate deficiency
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Health technology assessment reports, meta-analyses, systematic reviews (SR), and evidence-based guidelines were excluded if there was incomplete reporting of methodology or if they were superseded by a more recent, rigorous, or updated review or guideline. Randomized controlled trials and non-randomized studies were excluded if they were included by a selected SR. Economic evaluations that only reported costs and were not cost-effectiveness or cost-utility analyses were also excluded.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised. The included SRs were critically appraised using the AMSTAR checklist and the methods used when conducting the literature search, study selection, quality assessment, data extraction, and for summarizing the data were assessed.[20] Randomized and non-randomized studies were critically appraised using the Downs and Black checklist,[21] and appropriateness and external validity of cohorts, blinding, recruitment time-frames, losses to follow-up, consideration of confounders, and completeness of reporting were assessed. Guidelines were assessed with the AGREE II instrument.[22] The scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence were evaluated. Summary scores were not calculated for the included studies; rather, a narrative summary of the strengths and limitations of each included study is provided.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 538 citations were identified in the literature search. Following screening of titles and abstracts, 532 citations were excluded and six potentially relevant reports from the electronic search were retrieved for full-text review. Eighteen potentially relevant publications were retrieved from the grey literature search. Of these 24 potentially relevant articles, 12 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report.[13,23-33] The study selection process is detailed in the PRISMA flowchart (Appendix 1).

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Detailed study characteristics are summarized in Appendix 2.

Study Design

One SR,[13] two non-randomized studies,[23,24] and nine evidence-based guidelines[25-33] regarding folate testing were identified. The single SR,[13] concerned the clinical utility of folate testing and searched evidence published from 2002 to 2013. No list of included studies was provided but four guidelines and two retrospective studies were summarized in varying degrees of detail. It included a review of guidelines as well as clinical and cost evidence. The two non-randomized studies[23,24], published in 2013[23] and 2015,[24] were retrospective chart reviews carried out at large medical institutions that cover the clinical utility of folate testing. One non-randomized study[23] was described in the SR[13] but due to inadequate reporting it was also included separately in this review. Two evidence-based guidelines[28,31] included recommendations regarding which assay to use for folate testing, and all nine included recommendations regarding clinical indications for folate testing.[25-33]

Country of Origin

The single SR was conducted by authors in Australia.[13] The two non-randomized studies were conducted in the United States (US).[23,24] The evidence-based guidelines were developed by researchers in the United Kingdom,[28] US,[27,32] multiple European countries,[25,33] South Korea,[29] multinational locations,[30] and Canada,[26] though the Canadian guideline was adapted from a guideline originally developed in the US. All guidelines were published between 2010 and 2014.

Patient Population

The SR[13] concerned patients at risk for folate deficiency including both apparently healthy patients and those with chronic diseases linked to folate deficiency.[13] The two non-randomized studies included patients who underwent folate testing at large medical centers.[23,24] One study only included adults while the other did not specify age but did report that both inpatients and emergency department patients were included.[23] One study[23] specified indications for folate testing including hematological, neurocognitive, and dietary risk factors. The other study[24] did not specify indication. The evidence-based guidelines were geared towards patients at risk of folate deficiency,[28] with non-myeloid malignancies,[26] with Alzheimer's and non-Alzheimer's dementia,[25,29,31,33] with chronic kidney disease,[30] and bariatric surgery patients.[27,32]

Interventions and Comparators

All of the identified references evaluated folate testing (either serum, RBC folate, or both). Only the SR[13] specified comparators, including supplementation without testing, no testing, or in the case of comparing quality of testing, alternative folate assays.[13]

Outcomes

The SR[13] and both non-randomized studies[23,24] investigated the clinical utility of folate testing. Clinical utility outcomes of interest included improvement in health outcomes and evidence of change in medical management following folate testing. The SR[13] also investigated the comparative quality of various folate assays.

All of the evidence-based guidelines provided recommendations regarding the appropriate clinical indications for folate testing.[25-33] Several of the guidelines also discuss which folate assay (serum or RBC folate) is more appropriate for evaluating folate status.[28,31]

Summary of Critical Appraisal

A detailed description of the critical appraisal of individual studies is included in Appendix 3.

Systematic Reviews

The SR[13] set clear objectives but did not cite a published protocol. A comprehensive literature search was conducted on multiple databases as well as a grey literature search. However, the search was restricted to publications from 2002 onward and by language (English). No justification was given for the restricted search dates, so it is unclear whether potentially relevant evidence was not considered in formulation of results, and also reduces transparency due to the absence of clarity surrounding evidence synthesis. The primary concern was that no explicit list of included studies and study characteristics was provided. In general the review did not follow standard SR reporting format as set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Scientific quality was assessed with the National Health and Medical Research Council Dimensions of Evidence tool, and quality was taken into consideration in the formulation of conclusions. Quality of individual studies was not discussed explicitly. No pooling of results or assessment of publication bias was conducted. The review included disclosure of professional affiliations and funding sources none of which appeared to be industry-associated.

Non-Randomized Studies

The two non-randomized studies[23,24] were both based on health records; therefore, while they suffered from the typical limitations of retrospective studies including lack of randomization and blinding and possible misclassification bias, some design elements such as patient selection and follow-up did not pose a significant risk of bias. In terms of reporting, both studies stated their objectives, intervention, and study findings clearly. One study reported estimates of random variability and probability values,[24] but the other study did not as no group comparisons were conducted.[23] Neither study reported safety outcomes associated with folate testing. In addition, one study did not report demographic characteristics thoroughly.[24] As these were database linked studies, the external validity was reasonable for hospital patients in developed countries with folate fortification. One study conducted a thorough review of indications for folate testing in a subset of the total population but did not report demographic characteristics of this subgroup leading to unclear generalizability of these outcomes.[23] Neither study had the presence of design elements necessary to blind participants or assessors but the statistical analysis was appropriate and the main outcomes were measured appropriately. As both studies relied on chart data it is possible that a change in management may not have been recorded. Potential confounders were not considered in one study[23] and minimally assessed (i.e., age, body mass index, hematological profile, other micronutrient status, race, alcohol intake, use of supplements) in the context of group comparisons in the other, but did not include clinical conditions associated with folate deficiency.[24] Neither study disclosed a sample size calculation.

Evidence-Based Guidelines

There was substantial variation in the quality of evidence-based guidelines. Most guidelines had clearly described objectives,[25-33] target populations,[25-33] and explicitly stated health questions supporting their scope and purpose.[25,26,26-32] The clinical expertise represented on the guideline development groups and the target users were clearly stated by most guidelines,[25-27,29-33] but not all,[25,28,33] and included representation from multiple clinical specialties as well as methodological support. Specific health questions were not stated by one guideline.[33] Patient input was not sought by any of the guideline development teams but one guideline stated that patient preferences were considered when "a recommendation involves a substantial element of personal choice or values."[30] The level of rigour of development varied. While comprehensive search strategies were employed by all guideline development teams, it was unclear whether the search was truly systematic in several cases as the number of reviewers involved in screening, selection, and abstraction tasks was not disclosed.[25,27,28,32,33] Likewise, several guidelines failed to disclose their study selection methods[27,28,32,33] or disclose the number of reviewers involved in information synthesis.[27,28,32] Despite these drawbacks, the quality of evidence,[25-32] methods for formulating recommendations,[25-31,33] as well as consideration of risk-benefit profile, [25-33] linkage between recommendations and supporting evidence,[26-28,31] and a peer-review process[25-31,33] were present in the majority of guidelines. One guideline failed to declare a peer-review process,[32] and the direct linkage between evidence and recommendations was unclear in several.[25,32,33] In several cases it was clear that evidence search results did not include information to inform recommendations regarding folate testing, which relied on expert opinion.[29,30] Some guidelines[27,29-31,33] disclosed a plan and timeline for updating the review, though dates were unclear in several cases. The clarity of presentation of recommendations was good in most cases.[25,26,28-33] Key recommendations were embedded within text and not explicitly stated in some cases.[25,32,33] The area in which most[25,26,26-28,32,33] but not all[29-31] guidelines were lacking was applicability. Facilitators and barriers to implementation, implementation tools, and a method of monitoring or auditing impact were not described. In cases where these elements are missing the potential and measured impact of these guidelines on practice and the culture of folate testing is difficult to gauge. Also, the lack of patient input may have had consequences for the scope of the guidelines and relevance to the needs of patient populations at risk for folate deficiency. All guidelines disclosed funding sources and competing interests and while it was unclear whether views of guideline group members influenced recommendations (especially in the case of clinical consensus) no funding sources were of great concern (i.e., no manufacturers or purveyors of folate testing).

Summary of Findings

Detailed study findings are included in Appendix 4.

What is the diagnostic accuracy of red blood cell folate versus serum folate testing for identifying folate deficiency?

No literature was identified regarding the diagnostic accuracy of RBC folate versus serum folate testing for identifying folate deficiency; therefore, no summary can be provided.

What is the comparative clinical utility of red blood cell folate versus serum folate testing?

No literature was identified regarding the comparative clinical utility of RBC folate versus serum folate testing; therefore, no summary can be provided.

What is the clinical utility of folate testing?

One systematic review,[13] and two non-randomized studies[23,24] directly investigated the clinical utility of folate testing.

The SR[13] did not identify any prospective studies regarding the clinical utility of folate testing. Two retrospective studies included in the review did not provide evidence to support the clinical utility of folate testing in patients with anaemia or dementia, and inpatients and emergency department patients, based on lack of change in management.[13]

Both non-randomized studies[23,24] failed to observe a meaningful change in medical management of patients following deficient folate tests. One study[24] reported that 39 to 56% of patients with deficient folate results received replacement therapy with no explanation as to why some patients did not. The other study only identified 2 (0.1%) deficient folate tests and 7 (0.3%) low normal folate tests, overall. Neither deficient patient received a subsequent change in management.

What is the cost-effectiveness of folate testing?

No literature was identified regarding the cost-effectiveness of folate testing; therefore, no summary can be provided.

What are the evidence-based guidelines regarding appropriate indications for folate testing?

The SR[13] identified several guidelines suggesting that folate testing is indicated in patients with dementia, chronic fatigue syndrome/myalgic encephalomyelitis, patients with abnormal blood counts and those with suspected gastrointestinal disorders associated with malabsorption or malnutrition.

The evidence-based guidelines also recommend folate testing for patients with Alzheimer's disease[29,31,33] and other non-Alzheimer's dementia syndromes,[25,29,31] non-myeloid cancer patients at risk of anemia,[26] and CKD.[30]

Recommendations based on poor quality and low subjective factor impact evidence (based on study design, data analysis, and interpretation factors)[32] and weak recommendations based on low quality evidence[27] were made regarding bariatric surgery patients. One guideline recommended pre-partum folate testing for bariatric surgery patients who become pregnant post-surgery.[32] Folate testing was recommended for patients who screen negative for iron deficiency anemia during routine evaluation post-surgery.[32] Post-operative folate testing was also recommended for patients who undergo Roux-en-Y,[32] laparoscopic biliopancreatic diversion with or without duodenal switch,[27,32] gastric bypass,[27] and sleeve gastrectomy procedures.[27]

One guideline recommended that folate status be assessed in situations similar to vitamin B12 deficiency.[28] Based on the clinical indications listed this includes patients with anaemia, eating

disorders, autoimmune diseases, history of glossitis or mouth ulceration, history of peripheral neuropathy, poor proprioception, malabsorption syndromes, use of certain medications (e.g., metformin, proton pump inhibitors, and oral contraceptives), neurocognitive impairment, consuming diets low in animal sourced foods, and pregnant women.

What are the evidence-based guidelines regarding which assay to use for folate testing?

Two evidence-based guidelines were identified regarding the optimal analytical method for folate testing.[28,30] The UK guideline[28] reported that serum folate testing is sufficient unless there is a strong clinical suspicion of folate deficiency in spite of normal serum folate and vitamin B12 levels. The Kidney Disease Improving Global Outcomes guideline[30] recommended that serum folate be used for assessment in most cases unless serum levels are normal or if recent dietary intake could potentially influence results.

Limitations

Clinical Evidence

All of the direct evidence identified on clinical utility of folate testing was conducted in hospital settings. This limits generalizability to other clinical populations such as long-term care and community dwelling patients with conditions associated with folate deficiency. Thus, while clinical utility was not demonstrated in hospital patients in a folic acid fortified country, these results cannot be extrapolated to non-fortified regions and alternative populations with higher deficiency rates or risk.

There was discordance in the method of classifying folate deficiency (one study used a single cut-off and another used multiple) among the two non-randomized studies.[23,24] The cut-offs used to define folate deficiency have an impact on the rate of deficiency and consequently on the composition of the deficient population assessed for benefits of folate testing. This issue could have resulted in either over or underestimation of clinical utility. Future investigation into this cut-off disagreement and standardization is warranted as there is a lack of consensus on the topic.[24]

Due to the retrospective design of the non-randomized studies,[23,24] the temporality of testing and medical management (e.g., supplementation, clinical intervention) was unclear. This problem arises in the results of the Theisen-Toupal et al. study[23] in which one patient with deficiency was shown to be receiving supplementation prior to testing. It was suggested that the patient was at risk for folate deficiency, not due to lack of intervention, but potentially for other reasons (e.g., lack of compliance).[23] Inclusion of these patients in analysis may skew the results towards a null effect.

Guidelines

The clinical expertise of the guideline development groups was unclear in several cases. As many recommendations were based on expert consensus the credibility of recommendations developed by these groups is unclear.

The large majority of the guidelines did not include recommendations regarding folate testing informed by high quality evidence. In fact, many recommendations were based on clinical consensus or expert opinion alone. In some cases this may have been due to lacking evidence,

but in other cases limitations of the search may have resulted in relevant evidence not being considered. In addition, poor reporting of systematic review methodology, research questions and search and study selection methods limited transparency and reproducibility of several guidelines. There were also cases of unclear linkages between evidence and recommendations, which may detract from the credibility of some recommendations.

The indications embedded within the recommendations for folate testing from the evidence-based guidelines cannot be considered an exhaustive list. The absence of guidance on other populations at risk for folate related health outcomes (e.g., mothers with offspring at high risk of congenital malformations, methotrexate users) does not preclude them from being valid populations for folate testing; rather, there is no evidence-based guidance on these topics.

The guideline[28] that recommended folate testing for conditions similar to those tested for vitamin B12 deficiency did not discuss why folate testing was relevant for indications clearly only associated with vitamin B12 deficiency, such as pernicious anemia. The appropriateness of this general recommendation is unclear due to the lack of clarification, despite the strong recommendation being based on high quality evidence. It may relate to the potential for folate supplementation to mask neurological sequelae of vitamin B12 deficiency but this is unclear.

It should be noted that one guideline[27] used the terms folic acid and folate interchangeably. Folic acid refers to the synthetic form of folate that is used in many supplements and fortified products due to its enhanced stability and absorption. However, serum and RBC folate tests measure many folate vitamers; therefore, referring to folate testing as a folic acid test is inaccurate. Specific tests for folic acid levels do exist but are not common outside of the research setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report reviews evidence regarding the clinical utility, cost-effectiveness, and appropriate indications and optimal methods for folate testing. Limited evidence presented in one systematic review,[13] two non-randomized studies,[23,24] and nine evidence-based guidelines,[25-33] was identified on several of these topics. Guidance was provided on indications for testing but overall evidence is lacking on the usefulness of folate testing in the clinical arena.

None of the studies directly assessing the clinical utility of folate testing[13,23,24] reported evidence of patient related benefits subsequent to or associated with folate testing. Very few patients in hospital were identified to be folate deficient and there wasn't a universal change in patient management with the availability of information on folate status.[23,24] Furthermore, there was no evidence regarding changes in folate status and folate-related health outcomes following folate testing. There was also no evidence comparing the utility of targeted supplementation versus testing. Research on these topics would fill a knowledge gap. Further research on the clinical utility of folate testing in at-risk populations not included in the above studies such as long-term care patients and pregnant women may also be useful. At this time, the cost-effectiveness of folate testing compared to not testing or providing targeted supplementation is unclear. While there is a breadth of data on costs of folate testing suggesting substantial spending,[10,14,17] no formal economic evaluations were available for appraisal. Thus, the lack of evidence informing the resource implications of testing prevents the assessment of the financial benefits or harms of limiting folate testing in Canada. Clinical guidelines recommend that folate status be tested in at-risk individuals suffering from clinical conditions including dementia, chronic fatigue, gastrointestinal conditions associated with malabsorption or malnutrition, abnormal

hematological profiles, eating disorders, autoimmune diseases, neurocognitive impairment, chronic kidney disease, pregnancy, non-myeloid cancer, and various vitamin B12 deficiency associated conditions. Most of these indications have clear associations with folate deficiency, with the exception of the vitamin B12-specific disorders. Two guidelines recommend the use of serum folate over RBC folate. No evidence regarding the diagnostic accuracy of serum and RBC folate was identified but based on the higher cost and methodological drawbacks of RBC folate testing, a fasting serum folate test was suggested to be sufficient in most cases. Harmonization of folate testing methodology and deficiency classification methods may provide further clarification regarding the most appropriate diagnostic approach.

In conclusion, the limited evidence identified does not support folate testing in hospital populations in folic acid fortified regions. Evidence-based guidelines recommend testing for specific at-risk clinical populations, but rely heavily on poor quality evidence and expert consensus to support these claims. The lack of high quality studies and evidence to support guideline recommendations should be taken into account in interpretation of the report.

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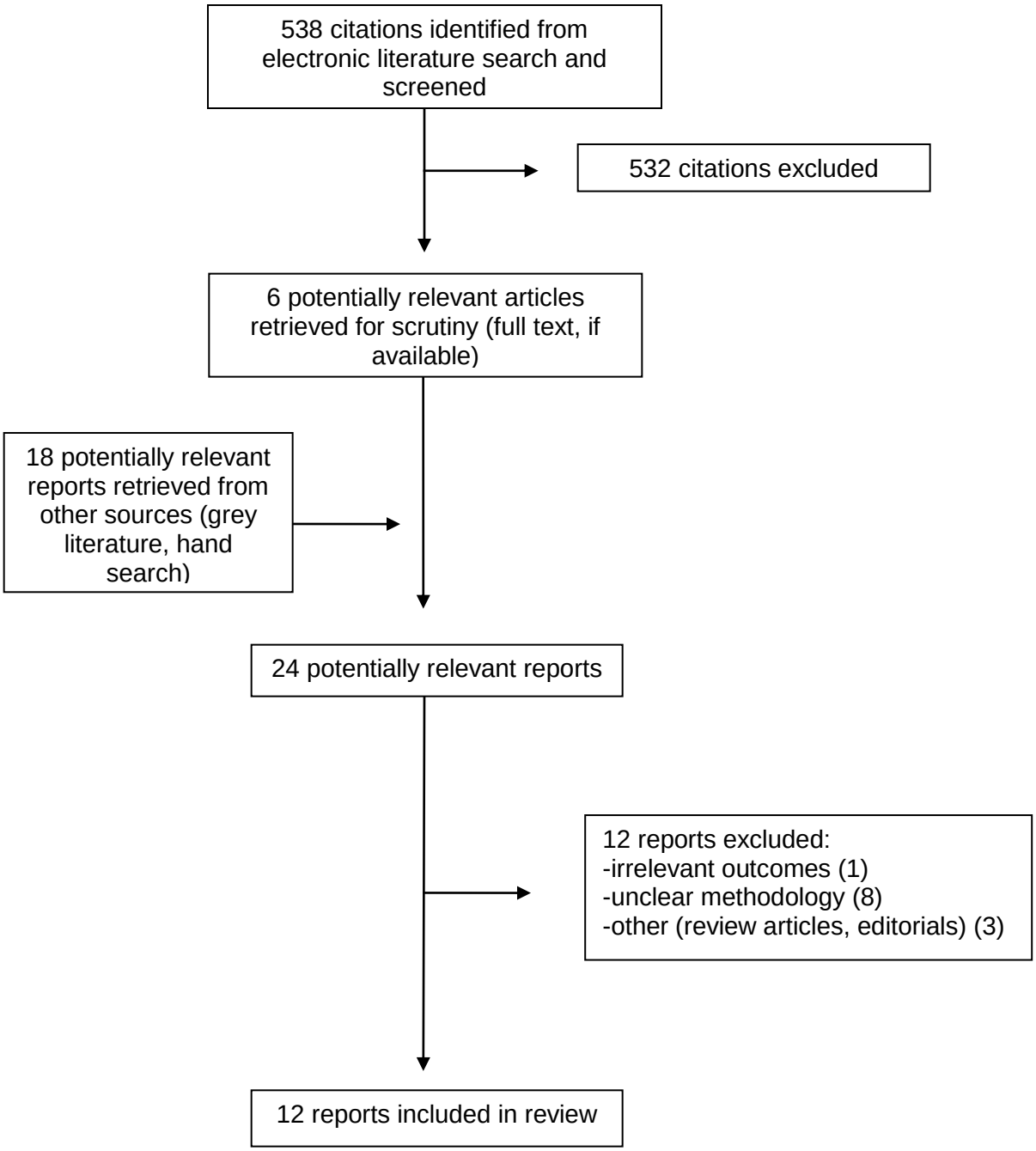
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
AGDH, 2014[13], Australia	Clinical guidelines, n = undisclosed*; Health technology assessments, systematic reviews, randomized controlled trials, prospective studies, n = 0; Non-randomized studies, n = undisclosed†; Safety studies, n = 0 Economic evaluations, n =0; Cost studies, n = 1	Patients at risk for folate deficiency: Apparently healthy populations (including pregnant women, elderly, vegetarians); Chronic disease linked to folate deficiency	Serum folate testing	Q1 to 3: Supplementation without testing, no testing or no comparator Q4: RBC folate testing	Q1: Indications for folate testing (guideline concordance) Q2: Improvement in health outcomes Q3: Risks and harms Q4: Quality of testing

AGDH = Australian Government Department of Health; RBC = red blood cell
*Four guidelines and reports are summarized in varying degrees of detail
†Two retrospective studies are summarized in varying degrees of detail

Table A2: Characteristics of Included Non-Randomized Studies					
First Author, Publication Year, Country	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Singh, 2015, US[24]	Retrospective chart review	Patients (n = 4448) (≥18 years) who underwent serum folate testing at tertiary care medical centers in Missouri and Georgia between July 2013 and July 2014	Serum folate testing (n = 5313) using chemiluminescent competitive binding protein assay (Beckman Coulter, Brea, CA)	N/A	Clinical utility (evidence of corrective action following deficient [serum folate <5.5 ng/mL] test result)
Theisen-Toupal, 2013, US[23]	Retrospective chart review	Inpatients (80%) and emergency department patients (20%) (n = 1944) who underwent serum folate testing at a large medical center in Boston, Massachusetts during 2011	Serum folate testing (n = 2093) using chemiluminescent competitive binding protein assay (Roche Diagnostics, Indianapolis, IN); 250 random chart reviews assessed	N/A	Clinical utility (change in management per deficient result)

RBC = red blood cell; US = United States

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
Devalia, 2014[28] *British Committee for Standards in Haematology*						
Health care practitioners; Patients with suspected cobalamin and folate disorders; UK	Folate testing	Guidelines regarding: Diagnosis and treatment of folate disorders Indications for folate testing; Use of serum	PubMed and Cochrane databases searched up to 2013; Selection and synthesis unclear	GRADE framework	Method of formulating recommendations unclear; Recommendations based on clinical judgement or consensus rather than objective evidence where evidence was	Reviewed by members of the General Haematology Task Force of the British Committee for Standards in Haematology, the guideline executive

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
		versus RBC folate			unavailable	committee, and a sounding board drawn from UK haematologists
Mechanik, 2014[32], *American Association of Clinical Endocrinologists, The Obesity Society, American Society for Metabolic & Bariatric Surgery (Update of 2008 guidelines)*						
Health care professionals (physicians and allied health professionals); Bariatric surgery patients; US	Perioperative nutritional, metabolic and nonsurgical support of the bariatric surgery patient • Folate testing in bariatric surgery patients	Indications for folate testing	Literature reviews (methodology unclear) and in areas of uncertainty, professional judgement	Ranked based on 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines. Evidence ratings based on type of study and evidence analysis and subjective factors assessed.	Grading of recommendations based on evidence level, subjective factor impact, consensus	Unclear
Choban, 2013[27], *American Society for Parenteral and Enteral Nutrition*						
Nutrition support clinicians; Obese adults who require nutrition support due to malabsorptive or restrictive	Folate testing	What micronutrients should be evaluated in the target patient group	SR including a search on PubMed, EMBASE and CINAHL up until May 2013	GRADE framework	Consensus process (considering strength of evidence, risks and benefits)	Unclear

Table A3: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
surgical procedures; US						
Sorbi, 2012[25], *European Federation of Neurological Societies – European Neurological Society*						
Clinical neurologists, geriatricians, psychiatrists and other specialist physicians in charge of care of patients with dementing disorders; Patients with non-Alzheimer's dementia; Various European countries	Folate testing	Blood tests required for clinical diagnosis of non-Alzheimer's dementia	Search for Cochrane reviews and other meta-analyses and SRs, evidence-based management guidelines and scientific papers published prior to 2011 in English	Evidence classified and consensus recommendations graded based on EFNS guidance[34] – where there was a lack of evidence but clear consensus and experiential knowledge good practice points were provided Articles were included based on consensus of the committee	Consensus was reached over the course of five revisions with participation by all EFNS panel members	Unclear
KDIGO, 2012,[30] *International Society of Nephrology*						
Chronic kidney disease patients at risk of anemia	Folate testing	Blood tests required for diagnosis, evaluation, and	Recommendations based on evidence retrieved using systematic literature	GRADE system used to rate quality of evidence and strength of	Recommendations or suggestions provided based on quality of evidence and	Unclear

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
		management of chronic kidney disease patients	searches	recommendations	consensus	
CRCDSK, 2011[29]						
Psychiatrics, neurologists, internists, family doctors and general physicians at secondary or tertiary care hospitals Patients with Alzheimer's disease, vascular dementia, mild cognitive impairment, and vascular cognitive impairment; South Korea	Folate testing	Laboratory tests required for the diagnosis of dementia	Adaptation was the main developmental method due to no previously available domestic guidelines (ADAPTE Collaboration methodology) Existing guidelines for care of dementia and relevant literature were searched (1997 to 2007) From 2007 onward multiple databases searched to retrieve primary articles of relevance which were selected by the steering committee based on relevance	AGREE evaluation of selected guidelines for adaptation	Evaluation of the key guidelines among existing CPGs, quality of guidelines, acceptability and applicability, timeliness, guidelines modified if necessary Revised CPG sent to 33 clinical research centers for dementia nationwide for assessment before external evaluation followed by a public hearing organized by National Clinical Research Coordination Centre of the Korean Centers for Disease Control	Official endorsement made by all dementia-related academic entities in South Korea during a public hearing
Hort, 2010[33], *European Federation of Neurological Societies*						
Clinical	Folate testing	Laboratory	Update of a 2007	Evidence from prior	Consensus	Unclear

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
neurologists, geriatricians, psychiatrists and other specialist physicians; Patients with Alzheimer's dementia; Various European countries		tests required for the diagnosis of Alzheimer's disease	guideline Search for evidence (unclear if systematic) performed on Cochrane Library and MEDLINE	to May 2009 was reviewed, and classified by level of certainty	recommendations were graded by strength of evidence according to EFNS guidance, or where evidence was unavailable but clear consensus achieved, good practice points were provided	
Ministry of Health, Social Services and Equality – Spanish National Health Service, 2010[31]						
Health professionals with direct contact with patients with dementia†, caregivers of people affected by dementia, people affected by dementia Patients with dementia disorders including Alzheimer's	Folate testing	Laboratory tests required for the diagnosis of Alzheimer's disease	Multiple databases searched from January 2006 to February 2009 in Spanish, Catalan, French, English and Italian (initially for CPGs and SRs, second phase for original studies) – search alerts until 2009	SIGN Levels of Evidence and Grades of Recommendation	Formal assessment of reasoned judgement of SIGN was used to formulate recommendations, where evidence unavailable consensus used	Unclear

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
disease, vascular dementia, Parkinson's Disease Dementia, dementia with Lewy bodies, and frontotemporal lobal degeneration; Spain						
Shehata, 2010[26], *Cancer Care Ontario**						
Healthcare practitioners treating patients with anemia and cancer; Patients with non-myeloid malignancies at risk for developing anemia receiving erythropoietic agents; Canada	Folate testing	Necessity of folate testing in patients with non-myeloid malignancies at risk for developing anemia	Use the methods of Practice Guidelines Development Cycle Expert panel formed to review and assess ASH/ASCO guideline (clinicians with expertise in the area of interest, members from the Hematology DSG and Systemic Therapy guideline development group and one methodologist.	Identified guidelines assessed for quality using the AGREE instrument (scope and purpose, stakeholder involvement, rigour of development, clarify of presentation, applicability, editorial independence)	Adopted or adapted from ASH/ASCO clinical practice guideline following review of the evidence-base and quality of the guideline	Unclear

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population, Country of Development	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendation Development and Evaluation**	**Guideline Validation**
(adaptation of US guideline)			5 SRs were used in the guideline development process as well as a search for clinical practice guidelines			

ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CRCDSK = Clinical Research Center for Dementia of South Korea; GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease, Improving Global Outcomes

*Original guideline from which this guideline was adapted published in 2007 by the American Society of Hematology and the American Society of Clinical Oncology

Note: Guideline scope may be broader than the objectives stated as only those relevant to folate testing are listed

†General practitioners, neurologists, geriatricians, psychiatrists, neuropsychologists, psychologists, nurses, pharmacists, internists, physiotherapists, occupational therapists, social workers), professionals from other areas that have direct contact with people affected by dementia (social services, media, justice)

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[20]

Strengths	Limitations
AGDH, 2014[13]	
• Clear review objectives set • Literature search performed on multiple databases; strategy provided • Grey literature search conducted • Scientific quality of studies assessed using National Health and Medical Research Council Dimensions of Evidence that assesses study on basis of strength of evidence, size of effect and relevance of evidence; these factors considered in formulation on conclusions† • Professional affiliations of committee members disclosed	• No review protocol published prior to conduct of review • Number of reviewers involved in screening and abstraction unclear • Search restricted to English language publications, 2002 onward • Number of publications retrieved and list of characteristics of included studies not provided • No pooling of studies discussed in methodology and reasons for foregoing unclear • Publication bias not considered • Funding sources unclear*

AGDH = Australian Government Department of Health; AMSTAR = Assessing the Methodological Qualities of Systematic Reviews
*Funding undisclosed but some affiliation with the Australian Government is implied
†See page 50 of report for detailed quality assessment methods

Table A5: Strengths and Limitations of Non-Randomized Studies using Downs and Black[21]

Strengths	Limitations
Singh, 2015[24]	
Reporting • Objective clearly described • Main outcomes described within methods • Intervention clearly described • Main study findings clearly described • Estimates of random variability presented • Database study; no loss to follow up • Probability values presented *External Validity* • Database study; population and environment representative of all inpatients and emergency department patients who received folate tests over the study period *Internal Validity - Bias* • Participants and assessors not blinded to intervention (folate testing) • No evidence of post-hoc analysis • Statistical analysis appropriate • Main outcome measures appropriate *Internal Validity – Confounding*	*Reporting* • Demographic characteristics of sample not reported; only differences in several characteristics between individuals with low and high serum folate • No distribution of confounders described • No safety outcomes presented *Internal Validity – Confounding* • Due to study design, randomization not possible and randomization concealment not relevant • Confounders were only considered in comparison of individuals with high and low folate *Power* • Sample size calculation not disclosed

Table A5: Strengths and Limitations of Non-Randomized Studies using Downs and Black[21]	
Strengths	**Limitations**
• All patients included from the same population over the same time period	
Theisen-Toupal, 2013[23]	
Reporting • Hypothesis clearly described • Main outcomes described within introduction and methods • Characteristics of included patients provided • Intervention clearly described • Main findings clearly described • Database study; no loss to follow up *External Validity* • Database study; population and environment representative of all inpatients and emergency department patients who received folate tests over the study period *Internal Validity – Bias* • Participants and assessors not blinded to intervention (folate testing) • No evidence of post-hoc analysis • Statistical analysis appropriate • Main outcome measures appropriate • Database study – no recall bias for exposure and all cases of folate testing likely to have been included *Internal Validity – Confounding* • Database study of all folate tests at one institution over a specified time period *Power* • *Power calculation not relevant as no group comparisons were made*	*Reporting* • No group comparisons made; therefore, no distribution of confounders or probability values presented • No variability estimates presented • No safety outcomes presented *External Validity* • Demographic characteristics of sub-group of random chart reviews unclear – generalizability limited • Limited generalizability to non-fortified regions and clinical populations not captured in the chart review *Internal Validity – Confounding* • Due to study design, randomization not possible and randomization concealment not relevant • No adjustment made for potential confounders *Other* • Only 259 charts reviewed for selections and indications in 93.6% • Folate supplementation not assessed in full study population

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
Devalia, 2014[28]	
Scope and Purpose • Aims of guideline specifically described • Applicable population is clearly described *Rigour of Development* • Comprehensive search conducted • Strengths and limitations of evidence clearly described • Methods for formulating recommendations clearly described • Risks-benefit profile considered in formulation of recommendations • Explicit link between recommendations and supporting evidence • Plan for updating stated • Guideline externally peer-reviewed prior to	*Scope and Purpose* • Health questions not explicitly stated, rather specific topics presented under headings *Stakeholder Involvement* • Expertise of the guideline development group unclear • Patient preferences not sought • Target users unclear *Rigour of Development* • Systematic nature of search and selection unclear • Plan for updating guideline very non-specific *Applicability*

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
publication *Clarity of Presentation* • Recommendations specific and unambiguous • Different options for management presented • Key recommendations easily identifiable *Editorial Independence* • Funding sources and competing interests disclosed • Views of guideline development group members unlikely to have influenced recommendations	• Facilitators and barriers not described • Implementation tools not provided • No monitoring or auditing criteria presented
Mechanik, 2014[32], American Association of Clinical Endocrinologists, The Obesity Society, American Society for Metabolic & bariatric Surgery	
Scope and Purpose • Objectives are specifically described • Health questions clearly listed • Target population and users of guideline are clear *Stakeholder Involvement* • Multiple clinical groups represented on guideline development group *Rigour of Development* • Guideline states that products are "systematically developed statements", and "most of the content herein is based on literature reviews." • Quality assessment of literature completed • Process for formulating recommendations not described – "Consensus among primary writers was obtained for each of the recommendations" • Risk-benefit profile considered throughout recommendations *Clarity of Presentation* • Clear and unambiguous recommendations • Management options for different types of surgery clearly presented *Editorial Independence* • Funding sources and competing interests of guideline development members have been disclosed	*Stakeholder Involvement* • Patient input not sought *Rigour of Development* • Search and selection strategy unclear • Strengths and limitations of included evidence not stated outside of final grading • Procedure for updating guideline not stated; however, guideline is an update of a 2008 version and they state that they follow National Guideline Clearinghouse guidelines for expiry timelines • Link between evidence and recommendations unclear • External peer review process unclear; however, it is stated in the methods that reviewers were selected *Clarity of Presentation* • Individual recommendations clearly defined; however, key recommendations embedded within text *Applicability* • Facilitators and barriers to application unclear • No tools or advice provided for implementation • No monitoring or auditing criteria presented
Choban, 2013[27], American Society for Parenteral and Enteral Nutrition	
Scope and Purpose • Objectives are specifically described • Health questions clearly listed • Target population and users of guideline are clear *Stakeholder Involvement* • Multiple clinical groups (medicine, nursing, pharmacy, dietetics, and nutrition science) represented on guideline development group *Rigour of Development* • SRs used to inform recommendations, clear methodology for guideline development presented	*Stakeholder Involvement* • Patient input not sought *Rigour of Development* • Search limited to ten years, English language publications • Study selection strategy unclear *Applicability* • Facilitators and barriers to application unclear • No tools or advice provided for implementation

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
• Search strategy clearly described; multiple databases searched • Quality assessment (GRADE) of literature completed • Process for formulating recommendations described clearly • Risk-benefit profile considered throughout recommendations • Link between evidence and recommendations clear • External peer-review process completed • Guideline will be updated in 2018 • Guideline submitted for final approval to A.S.P.E.N. board of directors *Clarity of Presentation* • Clear and unambiguous recommendations • Key recommendations clearly defined *Editorial Independence* • Project was unfunded	• No monitoring or auditing criteria presented *Editorial Independence* • Competing interests of authors unclear *Other* • General confusion throughout guideline regarding the terms folic acid and folate
Sorbi, 2012[25], EFNS-ENS	
Scope and Purpose • Objectives are specifically described • Health questions clearly listed • Target population and users of guideline are clear *Rigour of Development* • Search retrieved high quality evidence published before June, 2011 • Quality assessment of literature completed • Guideline peer-reviewed prior to publication • Risk-benefit profile considered throughout recommendations *Clarity of Presentation* • Clear and unambiguous recommendations *Editorial Independence* • Funding sources and competing interests of guideline development members have been disclosed	*Stakeholder Involvement* • Expertise of panel members unclear • Patient input not sought *Rigour of Development* • No evidence that the search and selection was systematic • Strengths and limitations considered • Procedure for updating guideline not stated • Link between evidence and recommendations unclear • Process of establishing recommendations clearly stated *Clarity of Presentation* • Individual recommendations clearly defined; however, key recommendations embedded within text *Applicability* • Facilitators and barriers to application unclear • No tools or advice provided for implementation • No monitoring or auditing criteria presented
KDIGO, 2012[30]	
Stakeholder Involvement • Guideline development group included individuals from all relevant clinical areas (internal medicine, adult and pediatric nephrology, cardiology, hematology, oncology, hypertension, pathology, pharmacology, epidemiology, and endocrinology) *Scope and Purpose* • Objectives are specifically described	*Stakeholder Involvement* • Patient input not sought; however, patient preferences considered when “a recommendation involves a substantial element of personal choice or values.” *Rigour of Development* • Plan for updating guideline presented; however, no date is set for updating –

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
• Health questions clearly listed • Target population and users of guideline are clear *Rigour of Development* • SR methodology used to retrieve evidence • Selection criteria clearly described in PICO format • Quality assessment of literature completed • Guideline peer-reviewed prior to publication • Strengths and limitations presented alongside recommendations • Risk-benefit profile considered throughout recommendations (net health benefit determined) *Clarity of Presentation* • Clear and unambiguous recommendations • Key recommendations clearly stated *Applicability* • Implementation considerations presented *Editorial Independence* • Funding sources and competing interests of guideline development members have been disclosed	stated that the results from ongoing studies will be reviewed periodically and may influence the decision to update the review • Evidence retrieved from the SR topics did not inform recommendations regarding folate testing • Only a single database was searched and no grey literature search was conducted • Process of establishing recommendations clearly stated *Applicability* • No actionable strategies provided for implementation • No monitoring or auditing criteria presented
CRCDSK, 2011[29]	
Stakeholder Involvement • Guideline development group included individuals from all relevant clinical areas (neurologists and psychiatrics, search experts, methodology experts and other stakeholders) • Public hearing organized for stakeholder feedback *Scope and Purpose* • Objectives are specifically described • Health questions clearly listed • Target population and users of guideline are clear *Rigour of Development* • Thorough search (multiple databases) and systematic methods for selecting existing guidelines to adapt • Selection criteria clearly described in PICO format • Quality assessment of literature completed • Guideline peer-reviewed by experts prior to publication • Plans for review and update presented • Risk-benefit profile considered throughout recommendations • Explicit link between recommendations and supporting evidence • Process of establishing recommendations clearly stated *Clarity of Presentation* • Clear and unambiguous recommendations • Key recommendations clearly stated *Applicability* • Implementation considerations presented • Implementation strategies and adaptation plans	*Stakeholder Involvement* • Patient input not sought *Rigour of Development* • Plan for updating guideline presented; however, no date is set for updating • Evidence retrieved from the SR topics did not inform recommendations regarding folate testing • Strengths and limitations of evidence not considered alongside recommendations *Applicability* • No monitoring or auditing criteria presented

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
presented *Editorial Independence* • Funding sources and competing interests of guideline development members have been disclosed	
Hort, 2010[33], EFNS	
Scope and Purpose • Overall objective clearly described • Target population specifically described *Stakeholder Involvement* • Target users specifically described *Rigour of Development* • Methods for formulating recommendations clearly described • Risk-benefit profile considered throughout recommendations • Guideline peer-reviewed prior to publication • Update was scheduled for 2012 *Clarity of Presentation* • Recommendations are clear and unambiguous • Key recommendations presented *Editorial Independence* • Funding sources and competing interests of guideline development group were disclosed	*Scope and Purpose* • Specific health questions not explicitly stated, but recommendations organized by topic *Stakeholder Involvement* • Expertise of guideline development group not explicitly stated • Patient input not sought *Rigour of Development* • Unclear if search was systematic • Selection criteria unclear • Link between recommendations and supporting evidence unclear • 2012 update of guideline could not be located *Clarity of Presentation* • Recommendations embedded within text; not easily identifiable *Applicability* • Facilitators and barriers to application unclear • No advice or tools for applying recommendations provided • Implications of applying recommendations unclear • No monitoring and/or auditing strategy presented
Ministry of Health, Social Services and Equality – Spanish National Health Service, 2010[31]	
Scope and Purpose • Overall objective clearly described • Health questions specifically described • Target population specifically described *Stakeholder Involvement* • Guideline development group included individuals from all relevant clinical areas (neuropsychiatrists, psychiatrists, neurologists, geriatricians, general practitioners, nurses, psychologists, neurologists, public health professionals, pharmacists, policy officials, oncologists, sociologists, social workers) • Target users of the guideline clearly defined *Rigour of Development* • Strengths and limitations clearly described • Method for formulating recommendations clearly described • Risk-benefit profile considered in formulation of recommendations	*Stakeholder Involvement* • Views and preferences of target population not sought *Rigour of Development* • Comprehensive search strategy employed; unclear if systematic • Plan for updating guideline (within 5 years) stated

Table A6: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
• Explicit link between recommendations and supporting evidence • Guideline was peer-reviewed prior to publication • Strengths and limitation clearly described • Methods for formulating recommendations clearly described *Clarity of Presentation* • Recommendations are specific and unambiguous • Key recommendations easily identifiable *Applicability* • Implementation strategy presented along with barriers and facilitators • Monitoring indicators proposed *Editorial Independence* • Funding sources and competing interests of guideline development group disclosed • Views of funding body did not affect guideline	
Shehata, 2010[26], Cancer Care Ontario*	
Scope and Purpose • Objectives are specifically described • Health questions described specifically • Target population specifically described *Stakeholder Involvement* • Multiple clinical groups represented on guideline development group • Target users clearly defined *Rigour of Development* • SRs used to inform recommendations, clear methodology for guideline development presented • Selection criteria stated (in PICO format) • Strengths and limitations of evidence considered • Methods for formulating recommendations described • Risk-benefit profile considered throughout recommendations • Explicit link between recommendations and supporting evidence • Peer review process conducted *Clarity of Presentation* • Recommendations specific and unambiguous • Different management options presented • Key recommendations clearly identifiable *Editorial Independence* • Funding sources and competing interests of the author's declared	*Stakeholder Involvement* • Patient input not sought *Rigour of Development* • Procedure for updating guideline not stated *Applicability* • Facilitators and barriers to application unclear • No tools or advice provided for implementation • No monitoring or auditing criteria presented

AGDH = Australian Government Department of Health; AGREE = Appraisal of Guidelines Research and Evaluation; A.S.P.E.N. = American Society for Parenteral and Enteral Nutrition; CRCDSK = Clinical Research Center for Dementia of South Korea; EFNS = European Federation of Neurological Societies; ENS = European Neurological Society; GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease, Improving Global Outcomes; PICO = patients, intervention(s), comparator(s), outcome(s)

*As part of the guideline adaptation process the committee scored the guideline using the AGREE Domain tool. Some quality assessment points were derived from this assessment.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
AGDH, 2014[13]	
• Based on existing clinical practice guidelines, recommendations have been made that folate testing should be included for patients with dementia, chronic fatigue syndrome/myalgic encephalomyelitis (following a full blood count analysis and mean cell volume indicative of macrocytosis), and for patients with low haemoglobin levels and high mean corpuscular volume or suspected gastrointestinal disorders causing malabsorption or suspected malnutrition of any cause. • No trials designed to directly measure risks and harms associated with folate testing identified. • Two retrospective studies identified on the clinical utility of folate testing; low utility (lack of change in management) observed for inpatients and emergency department patients or routine testing in clinical practice for patients with anaemia or dementia • One SR was identified comparing the effectiveness of serum versus RBC folate – serum folate appears to be superior on the basis of responsiveness to folate intake, predictive value for NTD risk, fewer analytical limitations, and demonstration that clinical outcome would not be altered by the addition of RBC folate • Very limited, poor quality evidence related to the cost of folate testing	• There is no direct evidence on the clinical utility, with respect to health outcomes, of folate testing; retrospective evidence suggests poor utility with regards to change in management • There are guidelines to suggest folate testing is indicated in patients with dementia, chronic fatigue syndrome/myalgic encephalomyelitis, patients with abnormal complete blood counts, and those with suspected gastrointestinal disorders associated with malabsorption or malnutrition • Serum folate appears to be less labor intensive, more responsive to dietary changes, and sufficient when performed in isolation compared to the addition of RBC folate

AGDH = Australian Government Department of Health; NTD = neural tube defect; RBC = red blood cell; SR = systematic review;

Table A8: Summary of Findings of Included Non-Randomized Studies	
Main Study Findings	**Author's Conclusions**
Singh, 2015[24]	
• Of the 36 patients with serum folate <3.4 ng/ML, 56% had documentation of subsequent replacement therapy (1.0 mg of folic acid or multivitamin tablet) • Of 226 patients with serum folate <5.5 ng/mL, 39% had documentation of subsequent replacement therapy • Observed some instances of folate testing in subjects who were already being supplemented (e.g. 82/218 of those with high serum folate levels)	• There was evidence of replacement therapy following folate testing in 39 to 56% of patients with low folate status, depending on the cut-off used • The author's report their dissatisfaction that only 39% of individuals with low serum folate levels were provided supplementation. • No information was given regarding the factors that led to the decision to supplement or not supplement • Authors recommend continuing to measure serum folate in tertiary care patients as it is a marker for malnutrition • No information on subsequent improvement in folate status
Theisen-Toupal, 2013[23]	

• Of the 250 randomly assessed chart reviews all had normal or high serum folate.
• Of all folate tests 0.1% (2 tests) were deficient, and 0.3% (7 tests) were low-normal), 71.1% were normal and 28.5% were high
• In the two deficient patients no change management was observed based on the deficient result
  ○ One patient already receiving supplementation and non-compliant
  ○ Second patient not receiving supplementation but no change in management noted
• Of 9 deficient or low-normal 8 had comorbid risk factors for folate deficiency
• Indications for testing included anemia with or without macrocytosis, delirium, malnutrition and peripheral neuropathy
• High occurrence of concurrent serum folate and vitamin B12 testing (85.2%)for indications specific to vitamin B12 deficiency (e.g. peripheral neuropathy)suggests lack of necessity of folate testing in these patients
	• Folate testing did not result in change in management in deficient patients
	• No evidence for requirement to assess serum folate levels for delirium, dementia, peripheral neuropathy, malnutrition or any other indication (depression, pancytopenia, other neuropathies, headache, lethargy, psychosis, anxiety, suicidal ideation, leukopenia, alcohol abuse, frequent falls, methotrexate use, syncope)
	• No information on subsequent improvement in folate status presented

Table A9: Summary of Findings of Included Evidence-Based Guidelines

Recommendations	Key Messages
Devalia, 2014[28]	
• "Routine **red cell folate** testing is not necessary because serum folate alone is sufficient in most cases" (Grade 1A – strong recommendation, high quality of evidence) • "In the presence of strong clinical suspicion of folate deficiency, despite a normal serum level, a **red cell folate** assay may be undertaken, having ruled out cobalamin deficiency" (Grade 2B – weak recommendation, moderate quality of evidence) • "**Folate status** is generally checked in clinical situations similar to those of cobalamin deficiency" (Grade 1A – strong recommendation high quality of evidence) ○ Listed clinical conditions include anaemia, diets with low animal sourced food content, eating disorders, autoimmune disease, history of glossitis or mouth ulceration, history of peripheral neuropathy, poor proprioception, malabsorption syndrome, use of proton pump inhibitors, metformin and oral contraceptives, pregnancy, and neurocognitive impairment in the elderly • "Consultation of the British National Formulary and Summary of Product Characteristics is recommended for clarifying any suspicion of low serum **folate** levels associated with prescribed medications"	• Serum folate testing is sufficient; red cell folate not required unless there is a strong clinical suspicion of deficiency in spite of normal serum levels and vitamin B12 • Folate status should be checked in situations similar to cobalamin deficiency
Mechanik, 2014[32], American Association of Clinical Endocrinologists, The Obesity Society, American Society for Metabolic & Bariatric Surgery*	

• "Patients who do become pregnant following bariatric surgery should have nutritional surveillance and laboratory screening for deficiency every trimester, including iron, **folate** and B12, calcium and fat soluble vitamins (Grade D)."
• "Nutritional anemias resulting from malabsorptive bariatric surgical procedures might also involve deficiencies in vitamin B12, **folate**, protein, copper, selenium, and zinc and should be evaluated when routine screening for iron deficiency anemia is negative (Grade C; BEL 3)."
• Perioperative Checklist for Bariatric Surgery states: "Nutrient screening with iron studies, B12 and **folic acid** (RBC folate, homocysteine, methylmalonic acid optional), and 25-vitamin D (vitamin A and E optional); consider more extensive testing in patients undergoing malabsorptive procedures based on symptoms and risks."
• **Folate testing** SHOULD be undertaken post-operatively for patients who have undergone laparoscopic Roux-en-Y gastric bypass and laparoscopic biliopancreatic diversion/duodenal switch but NOT laparoscopic adjustable gastric band or laparoscopic sleeve gastrectomy
	• Based on poor quality and low impact evidence the guideline suggests that folate testing should be conducted:
	  ○ In patients who become pregnant following bariatric surgery
	  ○ In patients who screen negative for iron deficiency anemia
	  ○ Peri-operatively for patients who undergo Roux-en-Y and laparoscopic biliopancreatic diversion/duodenal switch

Choban, 2013[27], American Society for Parenteral and Enteral Nutrition	
• 21 observational studies and 2 RCTs identified regarding comparison of serum levels of various micronutrients in cohorts treated with different bariatric surgery procedures • "Patients who have undergone sleeve gastrectomy, gastric bypass or biliopancreatic diversion ± duodenal switch have increased risk of nutrient deficiency. In acutely ill hospitalized patients with history of these procedures evaluation for evidence of depletion of iron, copper, zinc, selenium, thiamine, **folate**, and vitamins B12 and D is suggested as well as repletion of deficiency states. Recommendations: Weak, Evidence: Low • "Evaluation of folic acid, iron and 25-hydroxyvitamin D should be done annually."	• A weak recommendation based on low quality evidence proposes that evaluation of folate depletion recommended in patients who have undergone sleeve gastrectomy, gastric bypass or biliopancreatic diversion ± duodenal switch
Sorbi, 2012[25], EFNS-ENS	
• "Most expert opinion advises screening for vitamin B12, **folate**, thyroid-stimulating hormone calcium, glucose, complete blood cell	• For patients with non-Alzheimer's dementia screening for folate status is recommended

Table A9: Summary of Findings of Included Evidence-Based Guidelines	
Recommendations	**Key Messages**
count, renal and liver function abnormalities." • Recommendations: assessment of co-morbidity: "**Blood levels of folate**, vitamin B12, thyroid-stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function tests should be evaluated at the time of diagnosis and serological tests for syphilis, Borrelia, and HIV might also be needed in cases with atypical presentation or clinical features suggestive of these disorders (Good Practice Point)." *Based on evidence from a single evidence-based review*[35]	based on very limited evidence and expert opinion
KDIGO, 2012[30]	
• Investigation of anemia: "In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (Not Graded): Complete blood count (CBC), which should include hemoglobin concentration, red cell indices, white blood cell count and differential , and platelet count, Absolute reticulocyte count, Serum ferritin level, Serum transferrin saturation (TSAT), Serum vitamin B12 and **folate levels."** • "**Folate deficiency is best detected in most patients with serum folate level testing**; RBC folate levels can be measured when serum folate levels are equivocal or when there is concern that recent dietary intake may obscure underlying folate deficiency using serum levels alone."	• Folate testing should be included in the assessment of patients with CKD • Serum folate should be used in most cases instead of RBC folate unless levels are normal or recent dietary intake could influence results
CRCDSK, 2011[29]	
• Based on consensus from previously published guidelines: "Laboratory tests of dementia should include CBC, biochemical profile (electrolytes, blood glucose, calcium, renal function, and hepatic function), thyroid function, serum vitamin B12 and **folate levels**.	• Folate testing should be conducted in dementia patients
Hort, 2010[33], EFNS	
• "Most expert opinion advises to screen for vitamin B12, **folate**, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function abnormalities." • Recommendations for diagnosis: "**Blood levels of folate**, vitamin B12, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function tests should be evaluated at the time of diagnosis and serological tests for syphilis, Borrelia and HIV might also be needed in cases with atypical presentation or clinical features suggestive of these disorders (good practice point)	• In Alzheimer's dementia patients, folate testing should be conducted
Ministry of Health, Social Services and Equality – Spanish National Health Service, 2010[31]	
• Based on non-analytic studies such as case reports and case series as well as expert opinion: "The CPGs recommend including: Haemogram, thyroid stimulating hormone, electrolytes, calcium and glucose as recommendable tests in general to rule out potentially reversible causes of dementia and to screen comorbidities, and determine **folates**, B12, luetic or human immunodeficiency virus serology when it is suspected that these may have been altered due to clinical context." • Based on non-analytic studies such as case reports and case series as well as expert opinion, and extrapolated data from higher quality studies: "**The determination of folate levels can also be added, especially in patients with limited cereal intake and c levels**[†], **above all in older adults**."	• For patients with Alzheimer's disease and other dementias, folate testing should be conducted, particularly in patients with limited cereal intake and older adults
Shehata, 2010[26], Cancer Care Ontario	
• "At a minimum, one should take a thorough drug exposure history,	• For patients with non-myeloid cancer at risk

Table A9: Summary of Findings of Included Evidence-Based Guidelines	
Recommendations	**Key Messages**
carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, **folate**, and B12 deficiency where indicated, and assess for occult blood loss and renal insufficiency." • The Hematology Disease Site Group noted that recommendation was not based on firm evidence but was endorsed without modification as it was found to be practical and reflect current practice • All five reviewers strongly recommend the guideline for use in clinical practice	of anemia, folate testing should be conducted

CKD = chronic kidney disease; CPG = clinical practice guideline; CRCDSK = Clinical Research Center for Dementia of South Korea; EFNS = European Federation of Neurological Societies; ENS = European Neurological Society; GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease, Improving Global Outcomes; RBC = red blood cell

*See pages 60 and 62 for a detailed explanation of grading scores:[32] Grade D recommendations are based on no evidence or descriptive evidence, no or negative subjective factor impact, and two thirds expert consensus; Grade C recommendations are based on A) no evidence with high subjective factor impact, B) descriptive evidence with no subjective factor impact, or C) good-quality evidence with negative subjective factor impact, and two-thirds consensus in all cases.

†Note: no clarification regarding what 'c levels' refers to is made in the guideline. Do to the ambiguity this aspect of the recommendation is not discussed.

APPENDIX 5: Additional References of Potential Interest

Previous CADTH Reports

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